

**PHILIP MORRIS U.S.A.**  
**INTEROFFICE CORRESPONDENCE**  
**Richmond, Virginia**

**To:** Robin Kinser

**Date:** 5/14/99

**From:** Kathy Mitchell, Jennifer Amador

*Kathy Mitchell Jennifer Amador*

**Subject:** Literature review on smoking compensation/titration

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The Library collection was reviewed for books pertaining to smoking compensation/titration. The period covered by books includes 1978-1997. These books contain citations from as early as 1933.

*(Attachment 1)*

A 1997 article by Gerard Scherer, "Cigarette Smoking and Compensation: An Evaluation of the Literature" provides definitions and descriptions of the various methods of investigation as well as 154 references from 1936-1996. *(Full citation is given in Attachment 1)*

To obtain the most recent publications three strategies were used.

1. MEDLINE was searched for articles published after 1995 using the terms (smoking[MH] or nicotine[MH]) and (compensation or titration) not economics." MH refers to Medical Subject Heading. A set of 36 citations was obtained. Of these, only two were relevant and not included in Scherer's evaluation of the literature. *(Attachment 2)*
2. The following cited references were searched in SciSearch for publications after 1995.

Benowitz NL, "Smokers of low-yield cigarettes do not consume less nicotine." *New Eng. J. Med.* 1983, 309, 139-142.

McMorrow MJ, "Nicotine's role in smoking." *Psychological Bulletin* 1983, 93, 302-327.

Nil R, "Effects of different cigarette smoke yields on puffing and inhalation: Is the measurement of inhalation volumes relevant for smoke absorption." *Pharmacol. Biochem. Behav.* 1986, 24, 587-595.

Russell MAH, "Relation of nicotine yield of cigarettes to blood nicotine concentrations in smokers." *BMJ* 1980, 280, 972-976.

Petitti DB, "Evidence for compensation in smokers of low yield cigarettes." *Int. J. Epidemiol.* 1983, 12, 487-489.

Byrd GD, "Comparison of measured and FTC-predicted nicotine uptake in smokers." *Psychopharmacology* 1995, 122, 95-103.

Woodward M, "Self titration of nicotine: evidence from the Scottish Heart Health Study." *Addiction* 1993, 88, 821-830.

The resulting set included two relevant articles that were not included in Scherer's evaluation of the literature. These articles also included 191 and 134 references. *(Attachment 2)*

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3. The following authors were searched in SciSearch for articles published after 1994.

Byrd GD  
Robinson JH  
Frost G

A set of 65 citations was retrieved. Of these, two were relevant and were not included in Scherer's evaluation of the literature. (*Attachment 2*)

The American Cancer Society's website does contain a copy of the Massachusetts Department of Health 1997 Nicotine Disclosure Report. It compares results of nicotine yield using the FTC method of testing with the Massachusetts method of testing. It does not include any references. [www.cancer.org/bottomsearch.html](http://www.cancer.org/bottomsearch.html)

The Action on Smoking and Health's United Kingdom website has published a paper on compensation. The article includes 35 references as well as excerpts from tobacco industry documents.

Jarvis, Martin. "Why low-tar cigarettes don't work and how the tobacco industry fooled the smoking public." [www.ash.org.uk/papers/big-one.html](http://www.ash.org.uk/papers/big-one.html)

Attachments

cc: Frank Gullotta  
Jan Jones  
Don Leyden  
Kohji Takada  
Roger Walk  
Central Files

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**ATTACHMENT 1****Books in the Library collection containing information on compensation**

Effects of Nicotine on Biological Systems II. Edited by P.B.S. Clarke. 1995, pp.1-407.  
QP 801.N48 A23.

Measurement in the Analysis and Treatment of Smoking Behavior. (National Institute on Drug Abuse Research Monograph 48) 1983. BF 789.S6 M48  
Chapter- "Analysis of Reinforcement by Varying Smoke Component Concentrations."

Nicotine Addiction. Edited by C. Tracy Orleans and John Slade. 1993, pp. 35-36. RC 567 N5  
Short discussion of downward compensation. Also cites two conflicting studies regarding titration.

Nicotine Psychopharmacology. 1990, pp.374-418. RA 1242.N5 W87

Nicotine, Smoking and the Low Tar Programme. Edited by Nicholas Wald and Peter Froggat.  
1989, pp. 85-227. RA 1242.T6 W157  
Two sections entitled "Smoking Yields and Compensation" and "Determinants of Low Tar Smoking and of Compensation."

Pharmacological Adjuncts in Smoking Cessation. (National Institute on Drug Abuse Research Monograph 53) 1985 RC 567 G71  
Chapter- "Titration Hypothesis Revisited: Nicotine Gum Reduces Smoking Intensity."

Recent Advances in Tobacco Science, 23. Tobacco Chemists Research Conference, 1997.  
Scherer, Gerhard. "Cigarette Smoking and Compensation: A review of the literature" pp. 197-245. QK866.T6 T62

Smoking and Human Behavior. Edited by Tara Ney and Anthony Gale. 1989, BF 789.S6 N56  
Chapter- "Smoking Behavior: A Multivariate Process," pp. 199-221.

Smoking Behaviour. Edited by Raymond E. Thornton. 1978. BF 209.N52 I56  
Several chapters dealing with changes in smoking behavior as a result of changes in the cigarette itself. (more nicotine, reduced draw resistance, shorter length)

Surgeon General Report 1988. "Cigarette Smoking: Controlled Drug Self-Administration."

Tobacco Smoking. (International Agency for Research on Cancer Monographs on the evaluation of the carcinogenic risk of chemicals to humans v. 38) 1986. RC 273 I61.  
The chapter on Biological Data includes information on biomarkers as well as factors influencing the extent of inhalation.

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**ATTACHMENT 2****Recent references on compensation or titration****MEDLINE****A further study of FTC yield and nicotine absorption in smokers.**

Byrd GD, Davis RA, Caldwell WS, Robinson JH, deBethizy JD

*Psychopharmacology (Berl)* 1998 Oct;139(4):291-9

Research and Development, R.J. Reynolds Tobacco Company, Winston-Salem, NC 27102, USA. byrdg@rjrt.com

The relationship between nicotine yield as determined by the FTC method and nicotine absorption was examined in 72 smokers in a more rigorous repetition of a previous study of 33 smokers. For this study, 113 smokers evenly distributed across four FTC "tar" yield ranges were recruited, only 72 demonstrated reasonable compliance with the study criteria with regard to sample collections and cigarette brand style consistency. Subjects recorded the number of cigarettes smoked daily and collected a 24-h urine sample and a saliva sample on 3 consecutive days. Nicotine absorption was determined by monitoring urinary excretion of nicotine and its metabolites. In addition, saliva samples were monitored for cotinine using radioimmunoassay (RIA). The correlation of the relationship for nicotine absorbed per cigarette was positive and significant ( $r = 0.31$ ,  $P = 0.008$ ) but weaker than in the previous study. Only smokers in the highest yield range showed any statistical difference from smokers in the lower ranges. Our results suggest that FTC nicotine yield is weakly related to nicotine absorption and that smoker-controlled factors exert a great influence on the amount of nicotine absorbed by smokers. Compensation is substantial but incomplete for the minority (by market share) of smokers at the low end of the yield scale. It is uncertain how well any alternative set of machine parameters would predict nicotine absorption for the majority of smokers, even if it were more predictive for the small number of smokers at the lower yield part of the range.

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**Psychophysiological and subjective effects of cigarettes having varying nicotine yields but relatively constant 'tar' yields.**

Pritchard-WS; Robinson-JH; Guy-TD; Davis-RA; Stiles-MF

Psychophysiology Laboratory, Bowman Gray Technical Center 611-12, R.J. Reynolds Tobacco Company, Winston-Salem, N.C. 27102, USA.

Neuropsychobiology. 1996; 34(4): 208-21

AB: Thirty-two subjects were tested in five double-blind sessions-16 subjects in the morning (a.m.) following overnight smoking abstinence, and 16 in the afternoon (p.m.) following ad lib smoking. In each session, subjects smoked 1 of 5 cigarettes having the following FTC nicotine/'tar' yields in mg: 0.08/8.5, 0.17/9.1, 0.37/9.8, 0.48/9.8, and 0.74/10.4. On a pre- to postsmoking basis, blood nicotine and heart rate increased with nicotine yield. The effect of nicotine yield on changes in self-rated anxiety was an inverted-U function, but this effect was possibly confounded by baseline differences. The following effects on EEG spectral-band magnitude were also obtained: (1) nicotine yields  $\geq 0.17$  mg decreased delta; (2) nicotine yields of 0.37 and 0.48 mg decreased theta in a.m. subjects; (3) nicotine yields  $\geq 0.37$  mg decreased alpha, the effect being greater in a.m. subjects; (4) no effect of yield on beta 1 was obtained; (5) nicotine yields of 0.48 and 0.74 mg increased the Cz-minus-T5 differential in beta 2. Pre- to postsmoking changes in this measure of beta 2 were not correlated with either blood nicotine or anxiety.

**CITATION SEARCHES**

**Gender differences in the pharmacology of nicotine addiction.** Number of References: 191  
Benowitz NL (REPRINT) ; Hatsukami D

*Addiction Biology*, 1998, V3, N4 (OCT), P383-404

Abstract: Smoking rates have declined in recent years less rapidly in women than in men. More adolescent girls than boys are currently smoking. Quitting smoking is reported in many studies to be more difficult in women than in men. These observations suggest that there may be gender differences in the nature of nicotine addiction. Gender differences in various pharmacological processes involved in nicotine addiction are reviewed. Women take in less nicotine from smoking per cigarette than men but, because of slower metabolism, nicotine levels in the body for a given number of cigarettes per day are similar in male and female smokers. Women tend to be less sensitive to the discriminative effects of nicotine and tend to regulate nicotine intake less precisely than men. On the other hand, women appear to be more sensitive to the effects of nicotine in reducing negative affect and reducing body weight. There is a strong association between depression and smoking, and this association appears to be stronger in women than in men. Women tend to respond more to environmental cues associated with smoking than do men. Thus, several lines of evidence suggest that nicotine addiction is different in women than in men. Understanding the basis for gender differences may be of utility in individualizing and optimizing smoking cessation therapy.

**Cited References:**

... WOODWARD M, 1993, V88, P821, ADDICTION

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**The Role of Nicotine in Smoking-Behavior.** Number of References: 134  
Huber GL; Byrne B; Allen TG; Pandina RJ  
*Seminars Respiratory and Critical Care Medicine*, 1995, V16, N2 (Mar), p134-154  
Cited References:  
... WOODWARD M, 1993, V88, P821, ADDICTION

### AUTHOR SEARCHES

**Assessing the Sensory Role of Nicotine in Cigarette-Smoking**  
Pritchard WS; Robinson JH; Guy TD; Davis RA; Stiles MF  
*Psychopharmacology*, 1996, V127, N1 (SEP), P55-62

**Abstract:** Thirty-two subjects were tested in five double-blind sessions (16 subjects in the morning following overnight smoking abstinence, and 16 in the afternoon following ad-lib smoking). In each session, subjects smoked one of five experimental (EX) cigarettes having the following FTC nicotine/'tar' yields in mg: 0.08/8.5, 0.17/9.1, 0.37/9.8, 0.48/9.8, and 0.74/10.4. In a sixth session, subjects smoked a 0.71/8.6 commercial 'light' (CL) cigarette that was their usual brand. Before and after smoking, subjects subjectively rated their desire to smoke a cigarette of their usual brand and had blood samples drawn. Following smoking, subjects rated the cigarette on a variety of sensory dimensions; they also rated smoking satisfaction. Analysis of variance indicated that nicotine played an important sensory role for a variety of dimensions related to cigarette taste and sensory impact but not perceived draw. Principal-components analyses indicated that sensory factors were at least as important as nicotine pharmacology (indirectly indexed by the pre-to post-smoking rise in blood nicotine concentration) when considering smoking's overall effects on satisfaction, product acceptance, and reduction in desire to smoke.

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**Comparison of Measured and FTC-Predicted Nicotine Uptake in Smokers**

Byrd GD; Robinson JH; Caldwell WS; Debethizy JD

*Psychopharmacology*, 1995, V122, N2 (NOV), P95-103

**Abstract:** Cigarette smokers have a wide variety of "tar" and nicotine yields to choose from in the current market, ranging from 0.5 mg "tar" and less than 0.05 mg nicotine to 27 mg "tar" and 1.8 mg nicotine by the Federal Trade Commission (FTC) method. To understand better the relationship between FTC nicotine yields and actual nicotine uptake in smokers, we have studied nicotine uptake in 33 smokers of self-selected products representing four "tar" groupings: 1 mg "tar" (1MG), ultra-low "tar" (ULT), full-flavor low "tar" (FFLT), and full flavor (FF) cigarettes. These cigarette categories had mean FTC nicotine yields of 0.14, 0.49, 0.67, and 1.13 mg/cigarette, respectively. The subjects smoked their usual brand of cigarette ad libitum and provided a 24-h urine sample for total nicotine uptake analysis over a period during which the number of cigarettes smoked was recorded. Nicotine uptake was determined by monitoring urinary nicotine and its metabolites, including the glucuronide conjugates. Daily nicotine uptake was  $9.1 \pm 7.3$  mg (range 1-21 mg) for 1MG,  $19.2 \pm 10.0$  mg (range 4-42 mg) for ULT,  $21.8 \pm 19.4$  mg (range 13-38 mg) for FFLT, and  $37.1 \pm 14.4$  mg (range 21-60 mg) for FF smokers. On a per cigarette basis, yields were  $0.23 \pm 0.11$ ,  $0.56 \pm 0.23$ ,  $0.60 \pm 0.18$ , and  $1.19 \pm 0.43$  mg nicotine, respectively. Although individual variability was fairly large (CVs of 0.39-0.80), means for the different groups showed that lower FTC yield smokers not only absorb less nicotine per 24-h period, but also per cigarette smoked. These data suggest that nicotine uptake is a function of individual smoking behavior within product design limits. We conclude from these data that, while FTC yield cannot precisely predict nicotine uptake for an individual smoker, it is useful in predicting and comparing actual nicotine uptake by smokers who select cigarettes with a particular FTC yield.

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